Ifosfamide-induced Encephalopathy in Patients With Uterine Sarcoma

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SUMMARY

Objective: To report two cases of recurrent uterine sarcoma that developed ifosfamide-induced encephalopathy (IIE) with successful management.

Case Reports: The patient in the first case developed grade 4 toxicity and had a partial response after the fourth dose of intravenous methylene blue was administered. Full recovery occurred 4 days after the development of IIE. The patient in the second case, who had grade 3 toxicity, had completely recovered 32 hours after the first dose of thiamine.

Conclusion: Careful evaluation of patients with recurrent gynecologic cancers and vigilance during infusion of chemotherapeutic regimens are important in reducing the risk and timely management of IIE. Both methylene blue and thiamine appear to be effective treatments for IIE. [*Taiwan J Obstet Gynecol* 2010;49(1):77–80]

Key Words: encephalopathy, ifosfamide, methylene blue, neurotoxicity, thiamine

Introduction

Ifosfamide is an alkylating agent and isomer of cyclophosphamide. Ifosfamide is used extensively in different chemotherapeutic regimens to treat various malignancies, such as gynecologic, testicular, head and neck cancers, lymphomas, Ewing's sarcoma, and osteogenic sarcomas. Common adverse effects of ifosfamide include alopecia, nausea, vomiting, bone marrow suppression, and hemorrhagic cystitis. However, a specific side effect of ifosfamide is central nervous system toxicity, which occurs in 10–30% (mean, 12%) of patients after intravenous infusion [1]. The clinical presentation of ifosfamide-induced encephalopathy (IIE) toxicity ranges from mild somnolence, agitation, confusion, hallucinations, and deep coma, while the most common presentation is confusion [2,3]. Here, we report two patients with recurrent uterine sarcoma that developed IIE shortly after administration of chemotherapeutic regimens containing ifosfamide. The relevant clinical issues regarding the development, risk factors, clinical presentations, diagnosis, treatment, and prophylactic measures and outcomes of IIE are also discussed.

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Case Reports

Case 1

A 79-year-old woman with recurrent malignant mixed müllerian tumor of the uterus was admitted for a third cycle of chemotherapy consisting of carboplatin (area under the curve, 4), and ifosfamide (5 g/m^2). The patient had been treated with cisplatin, with a cumulative dose of more than 300 mg/m^2. Her physical examination revealed a bulky pelvic mass. The results of laboratory data included the following: hemoglobin, 9.3 g/dL; sodium, 128 mmol/L; potassium, 2.1 mmol/L; blood urea nitrogen, 31 mg/dL; serum creatinine, 2.3 mg/dL; and albumin 2.3 g/dL. Results of the remaining examinations were normal. After electrolyte supplementation and blood transfusion, she underwent a third cycle of chemotherapy. Three hours after

completion of ifosfamide given intravenously, she developed confusion, disorientation, and alternating intervals of alertness and stupor. Approximately 6 hours later, she became comatose and no longer opened her eyes to painful stimuli. According to the National Cancer Institute common toxicity criteria, this patient displayed grade IV toxicity [1]. No peripheral neurologic abnormalities were noted. Computed tomography of the brain was normal. After careful exclusion of other potential causes, a diagnosis of IIE was made. Treatment with intravenous methylene blue (MB), 50 mg every 4 hours, was initiated, and a total of six doses of MB were administered. Partial improvement in symptoms was noted after four doses of MB, including motor responses and opening of the eyes to painful stimulation. She had a full recovery from the IIE 4 days after the initiation of intravenous MB.

Case 2

A 56-year-old woman with recurrent endometrial stroma sarcoma of the uterus was admitted for a second cycle of chemotherapy using carboplatin (area under the curve, 5) and ifosfamide (5 g/m^2). Bulky pelvic masses were noted on physical examination. The results of laboratory examination included a blood urea nitrogen of 46 mg/dL, serum creatinine of 2.0 mg/dL, and serum albumin of 3.4 mg/dL. Results of the remaining laboratory examinations were normal. The patient had been previously treated with cisplatin with a cumulative dose of more than 480 mg/m^2. Seventeen hours after completion of intravenous infusion of ifosfamide, she developed prolonged daytime sleepiness, hallucinations, and severe disorientation (grade III encephalopathy). The results of cranial computed tomography and electroencephalography were normal. Infectious, metabolic and organic causes were carefully excluded. She was treated with 100 mg of thiamine given intravenously every 4 hours. A marked improvement in the patient's neurologic symptoms was noted 16 hours after beginning the thiamine treatment. She had full recovery 32 hours after the first dose of thiamine.

Discussion

Ifosfamide has been widely used both as a single agent and in combination therapy for a variety of soft tissue and gynecologic cancers. In the registered Gynecologic Oncology Group trials and reported cases, ifosfamide has been used for previously treated or recurrent ovarian epithelial tumors, squamous carcinoma of the cervix, trophoblastic disease, and advanced or recurrent uterine sarcomas [4–7]. Ifosfamide is a prodrug metabolized by cytochrome P450 to its active alkylating agents, 4-hydroxy-ifosfamide and ifosfamide mustard. The selective dechloroethylation of ifosfamide leads to the release of the neurotoxic molecule chloroacetaldehyde. Other non-alkylating metabolites are also formed and may be responsible for the toxicity of the drug [2]. Cyclophosphamide does not exhibit neurotoxicity.

The exact pathophysiologic mechanisms for development of IIE have been related to the accumulation of various degradation products such as chloroacetaldehyde. Chloroacetaldehyde can cross the blood–brain barrier and is a potential neurotoxic substance [2]. Based on the findings of glutaric acid and sarcosine in the urine of a patient with IIE, Kupfer et al [8] hypothesized possible pathways by which ifosfamide metabolites could induce neurotoxicity. These biochemical abnormalities are similar to those of patients with glutaric aciduria type II, a disorder of mitochondrial fatty acid oxidation [8]. Subsequent investigations revealed that chloroethylamine may be another neurotoxic metabolite of ifosfamide [2]. The metabolites of chloroethylamine can inhibit the electron-binding flavoproteins in the mitochondrial respiratory chain, which may also lead to a disturbance of the intracellular nicotinamide adenine dinucleotide–reduced nicotinamide adenine dinucleotide balance, with the accumulation of nicotinamide adenine dinucleotide. This in turn prevents the dehydrogenation of aldehydes, such as the ifosfamide metabolite, chloroacetaldehyde, which requires nicotinamide adenine dinucleotide for oxidation.

IIE is not an uncommon side effect occurring in 10–30% (mean, 12%) of patients following intravenous infusion of ifosfamide. However, grade 3 and grade 4 toxicity accounted for 16.2% of patients [9]. The reported risk factors for the development of IIE were hypoalbuminemia, elevated serum creatinine level, hepatic insufficiency, the presence of tumors in the lower abdomen and pelvis, poorer performance status prior to treatment, previous or concomitant treatment with cisplatin, prior central nervous system disease, and advanced age [1]. Greater incidence of neurotoxicity had been observed in higher doses and shorter duration intravenous administration, suggesting a relationship with maximum plasma concentration. However, a retrospective cohort study by David and Picus [3] reported that the role of peak ifosfamide concentration, increased serum creatinine, and bulky abdominal disease as risk factors for IIE are controversial, with the dose-toxicity relationship, infusion rate, or infusion duration of ifosfamide not being significantly different between control subjects and patients who developed encephalopathy.

Impaired renal function may indicate a role for renal metabolism and/or excretion of the various causative agents of encephalopathy. Bulky pelvic tumors may be associated with some degrees of obstructive nephropathy, further deteriorating renal function. Previous cumulative dosages of cisplatin may be related to the decreased clearance of ifosfamide or its active metabolites owing to cisplatin-induced renal tubular damage [1]. In gynecologic cancers settings, impaired renal function, bulky tumors in the pelvis, and pretreatment with cisplatin and hypoalbuminemia are common potential risk factors that warrant particular caution while administering ifosfamide.

IIE is essentially a clinical diagnosis. Onset of encephalopathy ranges from 12 to 146 hours after beginning of infusion [10]. No electroencephalography or radiographic changes specific to this condition have been identified [3]. According to the National Cancer Institute common toxicity criteria, IIE is classified into four grades. Grade 1 is represented by dazed or slightly depressive periods, grade 2 neurotoxicity is marked by extensive sleep or agitation, grade 3 toxicity is determined by heavy depression, mild hallucinations or a stuporous condition, and grade 4 encephalopathy is diagnosed in patients with manifested state of hallucinations or coma.

The first use of MB for the treatment and prophylaxis of IIE was reported by Kupfer et al in 1994 [11]. Intravenous thiamine infusion in the management of IIE has also been suggested [1]. MB exhibits several synergistic modes of action, which overcome the dose-limiting neurotoxicity induced by ifosfamide [8]. MB may act as an alternative electron acceptor, replacing the inhibited flavoproteins and thus restoring the mitochondrial respiratory chain [12]. MB may also oxidize nicotinamide adenine dinucleotide, allowing dehydrogenation of aldehydes [13]. IIE is treated with MB 50 mg (1% aqueous solution over 5 minutes), six times daily [2]. The neurologic features of ifosfamide are akin to Wernicke encephalopathy, which is caused by severe thiamine deficiency often related to alcoholism. Management of IIE with intravenous thiamine is usually given at 100 mg diluted in 100 mL of normal saline, as a 10-minute infusion every 4 hours until resolution or significant improvement of symptoms [1,14]. The side effect of MB, at doses exceeding 4 mg/kg, may cause hemolytic anemia, and blue-green discoloration of the urine and feces [15]. The side effects of thiamine are uncommon and include local irritation, itching, sweating, and nausea [14]. There is no evidence suggesting that one is superior to the other.

Intravenous infusion of albumin is thought to act by binding chloroacetaldehyde, thereby preventing it from crossing the blood–brain barrier. Hemodialysis can remove ifosfamide and its metabolites and has been shown to reverse encephalopathy [16]. Glucose infusion has also been shown to be another effective option in the treatment of IIE [17]. Prophylactic measures can be applied in patients who are at high risk or have had IIE during prior therapy. MB (50 mg) can be given orally or intravenously 3–4 times a day, starting the first dose on the day before the beginning of chemotherapy. Thiamine (100 mg) can be given three times a day during chemotherapy [18].

The neurotoxicity of ifosfamide is generally self-limiting and reversible between 12 and 72 hours. However, encephalopathy can, in rare cases, result in patient death [19]. In conclusion, ifosfamide is widely used in chemotherapeutic regimens in gynecologic cancers. Gynecologic oncologists should be especially aware of the neuropsychiatric complications of ifosfamide when treating progression or recurrence of uterine, cervical or ovarian cancers. It is, therefore, important to recognize patients at risk for IIE, to objectively monitor patient responses, and to determine appropriate management, such as discontinuation of ifosfamide or prophylactic use and treatment with MB or thiamine.

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